



Dissociation of Blood Volume and Flow in Regulation of Salt and Water Balance in Burn Patients

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The relationship between effective blood volume and related hormones in burn patients following resuscitation is not well understood. Previous reports have suggested that hormone secretion is altered by a resetting of neural control mechanisms. Serum and urine sodium, plasma renin activity, serum ADH, cardiac index, effective renal plasma flow, and total blood volume were measured in seven burn patients (mean age, total burn size, and postburn day: 32 years, 56%, and 9 days, respectively). The same values (with the exception of cardiac index and blood volume) were measured in 10 control patients (mean age, 24 years). The blood volume of patients was measured by $^{51}\text{chromium}$ red blood cell (RBC) labeling and compared to normal predicted values based on body surface area and sex. Mean serum sodium and osmolality were 138 mmol/L (millimolar) and 286 mosm/kg, respectively, in both patients and control subjects. Mean \pm standard error of the mean total blood volume in the patients was low, $81\% \pm 4\%$ of predicted values. Cardiac index and renal plasma flow were significantly elevated. Plasma renin activity and antidiuretic hormone (ADH) levels were elevated and altered in the direction expected from blood volume measurements despite the findings of increased blood flow. Dissociation of organ flow and hormonal response suggests that simultaneous direct blood volume measurements are necessary to elucidate factors other than altered neural control settings to explain hormonal changes in the flow phase of injury. Depressed total blood volume appears to promote elevated ADH levels in burn patients following resuscitation. Whether there is an additional role of altered neural control settings remains to be established.

FACTORS RESPONSIBLE FOR sodium and blood volume regulation following injury are not clearly understood. Several authors have interpreted their

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data to imply that resetting of hormonal control mechanisms occurs following thermal injury and that this is a stress response that is not sodium or volume dependent.^{1,2} Although various studies have examined one or two factors responsible for sodium and volume regulation following thermal injury, no one has studied this system as a whole.

Antidiuretic hormone (ADH) response following thermal injury has been examined recently.²⁻⁴ Morgan et al.² have concluded that ADH levels were elevated after burn and remained so for 7 to 10 days. In addition the increased ADH levels appeared to have little relation to serum osmolality and did not affect urine output. Shirani et al.³ observed elevated plasma ADH levels in association with hyponatremia in burn patients even beyond the first 10 days. Those results were interpreted as being consistent with the diagnosis of the Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH). However in those studies blood or plasma volumes were not measured simultaneously with the measurement of ADH.

The renin-angiotensin-aldosterone axis has been examined following thermal injury.¹ Shirani et al.³ suggested that the elevated plasma levels of renin activity, angiotensin I, angiotensin II, and aldosterone following thermal injury reflected a resetting of hormonal control and did not depend on an effective plasma volume deficit. No volume measurements were made in that study. In that group of patients, combinations of these hormones remained volume responsive, as verified by saline-loading tests.

Atrial natriuretic factor (ANF), a family of potent natriuretic and diuretic peptides, are present in mammalian cardiac atria. Central hypervolemia and increased blood

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pressure have been postulated as factors that promote ANF secretion.⁵ An elevation of ANF has been shown to blunt aldosterone response to stimulation by angiotensin II.⁶ The effect of thermal injury on plasma ANF levels and how it, in turn, affects salt and water balance has not been described.

To define more precisely the mechanisms that regulate salt and water balance following thermal injury, we assessed plasma levels of ADH, ANF, and the renin-angiotensin-aldosterone axis simultaneously with measurement of blood volume and osmolality in burn patients 5 to 16 days after burn.

Materials and Methods

Ten healthy control subjects (seven men, three women) and seven burn patients (six men, one woman) whose characteristics are detailed in Table 1 were each studied during a 5-hour period, with blood and urine samples collected hourly for determination of electrolytes and creatinine. Controls were allowed to eat nothing by mouth beginning at 00:00 hours on the day of the study while the patients' enteral feedings were continued but oral intake was held. The patients' intravenous fluids were administered at a rate to maintain adequate urine output while allowing for an approximate 10% daily loss of the weight gain from initial resuscitation. The rate of fluid administration in the controls was matched to the mean patient hourly intake. Five patients weighed more than the preburn weight, while two weighed less than the preburn weight on the day of study (Table 1). The mean values during the study period were used as data for each patient. After a tracer bolus injection of ¹³¹I-hippuran (I-HIP) at the second hour (09:00 hours), additional blood samples were taken to characterize I-HIP decay in the plasma. Just before injection of the I-HIP, a plasma or serum sample was taken for determination of hormone concentrations. Cardiac index (CI) was determined by thermodilution at intervals during the study and blood volumes were determined with ⁵¹Cr-tagged autologous red cells at the end of the study period. Neither CI nor blood volumes were measured in control subjects.

Sodium and potassium were determined by flame pho-

tometry and osmolality by freezing-point depression. Urinary excretion rates and clearances were normalized to 1.73 m² body surface area (BSA): square root of [(height in cm × weight in kg)/3600].^{7,8} Preburn weight was used to express variables requiring body weight.

After injection of I-HIP, plasma samples were taken at 5, 10, 15, 20, 40, 50, 60, 70, 80, 100, and 120 minutes for counting in a gamma scintillation detector and determination of effective renal plasma flow.⁹ Effective renal plasma flow was calculated as the clearance of I-HIP by fitting the plasma ¹³¹I radioactivity to a biexponential expression of time after the dose [$a_1 \exp(b_1 \text{time}) + a_2 \exp(b_2 \text{time})$] and determining the dose of ¹³¹I counted in dilution separately [clearance = $-\text{dose}/(a_1/b_1 + a_2/b_2)$].

A ⁵¹Cr-tagged red cell method using an f-cell correction of 0.87 and the peripheral hematocrit was used to estimate whole blood (Bvol) and plasma (Pvol) volumes from the red cell volume (RBCvol).^{10,11} These volumes (measured in milliliters) were compared with those predicted as normal¹⁰ on the basis of sex and body size (male subjects: $\text{RBCvol} = 1486 \text{ BSA}^2 - 4106 \text{ BSA} + 4514$; $\text{Pvol} = 995 \exp(6085 \text{ BSA})$; female subjects: $\text{RBCvol} = 1167 \text{ BSA} - 479$; $\text{Pvol} = 1278 \text{ BSA}^{1.289}$; predicted Bvol was the sum of the predicted RBCvol and Pvol). If the mean observed/predicted ratio \pm the 95% or 99% confidence interval of the mean for the patients did not overlap 1, the respective (0.05 or 0.01) significance level was determined. Formulas¹² for direct prediction of expected normal Bvol based on sex and body size yielded values very close to the sum of predicted RBCvol + Pvol and did not alter the results.

Cortisol, aldosterone, ADH, and ANF were determined by radioimmunoassay (RIA) at the Nichols Institute, San Juan Capistrano, California, where plasma renin activity (PRA, RIA of generated angiotensin I) and corticotrophin (ACTH, two-site immunoradiometry) were also determined. Hormone values were above the detectable limits except for ADH in five controls, in whom the ADH value was recorded as 1 pg/mL, the least detectable value.

Data were analyzed using BMDP software¹³ (BMDP statistical software, Los Angeles, CA) on a Vax 3400 computer (Digital Equipment, Maynard, MA). The nonrectilinear regression (P3R) program was used to determine the parameters of the fit of plasma ¹³¹I to time after injection of I-HIP. The P7D program was used to compare variables between burns and controls with the t test.

Results

As expected several hemodynamic variables differed significantly between the two groups in a manner consistent with the hyperdynamic response to injury (Table 2). The patients were tachycardic, with a widened pulse pressure. Flow variables (effective renal plasma flow and CI) were significantly increased in patients (Table 2).

TABLE 1. Demographic Variables

Variable	Control	Patients
Age (years)	23.8 \pm 1.4*	32.4 \pm 5.8 (18–64)†
BSA (M ²)	1.89 \pm .08	1.88 \pm 0.05
TBSB (%)	—	56.1 \pm 5.3 (30–77.5)†
PBD (days)	—	8.7 \pm 1.5 (5–16)†
% PBW	—	103.4 \pm 3.14% (90.5–112.3)†

* Mean \pm SEM

† Range.

BSA, body surface area; TBSB, total body surface burn; PBD, postburn day of study; % PBW, % preburn weight.

TABLE 2. Hemodynamic Variables

Variable	Control	Patients
HR (bpm)	62 ± 6*	119 ± 3§
MBP (mmHg)	83 ± 3	77 ± 3
PP (mmHg)	45 ± 3	58 ± 4†
ERPF (mL/min/1.73 m ²)	525 ± 26	774 ± 96‡
CI (L/min/m ²)	[norm 2.3–4.1]	7.78 ± 0.52§

HR, heart rate; MBP, mean blood pressure; PP, pulse pressure; ERPF, effective renal plasma flow measure by ¹³¹I Hippuran; CI, cardiac index.

* Mean ± SEM.

† p < 0.05; ‡ p < 0.01; § p < 0.001.

The patients' RBC volumes measured by ⁵¹Chromium-labeled red blood cells were significantly less than predicted. Plasma volumes were 100% of the predicted values based on body surface area, while total blood volumes were 81% of the mean predicted values (Fig. 1). Because the observed/predicted total blood volumes had a wide variance (95% confidence limits of this value range from 70% to 92% for this patient population), patient values were also compared to the laboratory reference normal range for blood volumes based on body weight. Three patients had total blood volume measurements that were within the reference normal range, while four patients (two measured twice) had total blood volumes that were less than the lower value of the normal range (Table 3).

Mean plasma sodium and osmolality were identical for the two groups (Table 4). Urine flow was significantly greater in control subjects, while urine osmolality was significantly greater in the patients, despite similar intravenous fluid administration rates. Free water clearance was 2.43 mL/min/1.73 m² in controls and -1.65 mL/min/1.73 m² in patients. Elevated urinary potassium concentrations and K⁺/Na⁺ ratios were noted in the patients in association with slightly lower serum potassium levels and nondepressed urinary sodium values (Table 4).

Hormone values for patients and controls are tabulated

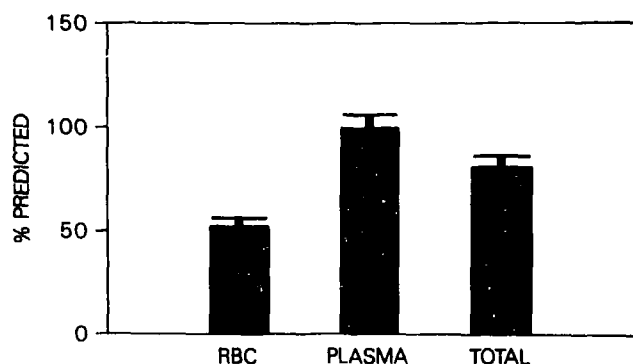


FIG. 1. The percentage of predicted red cell volume (RCV), plasma volume (PV), and total blood volume (TBV) for all patients is depicted. The RCV and TBV differs significantly from predicted values ($p < 0.01$), while calculated plasma volume was normal.

TABLE 3. Total Blood Volume

Patient	PBD	TBV (mL/kg)	Reference Normal Range (mL/kg)
1	5	51.14	60–80
1	12	55.64	60–80
2	7	56.90	60–80
3	10	68.34	60–80
4	6	46.00	55–75 (female)
4	10	53.37	55–75 (female)
5	16	61.61	60–80
6	11	47.11	60–80
7	6	63.97	60–80

The second measurement in patients 1 and 4 are not included in the data of Figure 1.

Abbreviations are defined in Tables 1 and 2.

in Table 5. AM cortisol levels were significantly greater in patients, as expected, while patient ACTH levels were not elevated. Plasma renin activity, ADH, and atrial natriuretic peptide levels were significantly greater in patients. Plasma aldosterone levels tended to be greater in patients but not significantly so when compared to the control population. Antidiuretic hormone levels were normal for the three patients with normal blood volumes and elevated for the four patients with decreased blood volumes ($p = 0.05$) (Table 6).

Discussion

Altered neural set points controlling the release of ADH and the renin-angiotensin-aldosterone axis have been invoked as an explanation for the elevated levels of these hormones, which are characteristic of the postresuscitative phase of burn care. Previous reports by Soroff et al.,¹⁴ Collentine et al.,¹⁵ Dolocek,¹⁶ and Shirani et al.¹ have all assumed that the findings of significant sodium excretion and urine flow, hyponatremia in some patients, low or normal plasma osmolality, and elevated blood flow as

TABLE 4. Serum and Urine Levels

	Controls	Patients
Plasma Na ⁺ (mmol/L)	137.5 ± 0.8*	137.7 ± 1.5
Urine Na ⁺ (mmol/L)	39.1 ± 4.5	70.0 ± 22.4
Na ⁺ excretion (meq/hr/1.73 m ²)	11.5 ± 1.0	7.8 ± 3.5
Plasma K ⁺ (mmol/L)	4.52 ± .09	3.96 ± 0.12‡
Urine K ⁺ (mmol/L)	8.9 ± 0.9	52.3 ± 6.3§
Urine K ⁺ /Na ⁺	0.24 ± 0.03	14.3 ± 9.2†
Plasma OSM (mosm/kg)	286 ± 1	286 ± 6
Urine OSM (mosm/kg)	160 ± 12	656 ± 45§
Urine output (mL/hr/1.73 m ²)	303 ± 19	87 ± 15§
FWCL (mL/min/1.73 m ²)	2.43 ± 0.3	-1.65 ± 0.15§
Intake (mL/hr)	250	284 ± 32

FWCL, free water clearance.

* Mean ± SEM.

† p < 0.05; ‡ p < 0.01; § p < 0.001.

TABLE 5. Hormone Values

Value	Controls	Patients
ACTH (pg/mL)	27.6 ± 5.7	13.0 ± 2.2
Cortisol (g/dL)	10.8 ± 1.1	22.6 ± 2.8†
PRA (ng/mL/hr)	1.3 ± 0.3	28 ± 8‡
Aldosterone (ng/dL)	4.2 ± 1.4	11.7 ± 5.6
ADH (pg/mL)	1.2 ± 0.1	5.6 ± 2.5*
ANF (pg/mL)	78 ± 6	167 ± 34†

* p < 0.05; † p < 0.01; ‡ p < 0.001.

indexed by increased glomerular filtration rates and cardiac output are an indication of normal or increased blood volume. These findings, in combination with less than maximally dilute urine and elevated plasma levels of ADH, have led to the diagnosis of SIADH. The apparent dissociation of blood volume and flow indices documented in our patients indicates that the finding of increased flow may not support the assumption that a volume factor is absent in burn-induced SIADH, especially when plasma ADH and urine tonicity are high, even in the setting of a low plasma tonicity. Thus it is possible that if free water delivery is high enough, low blood volume-induced ADH secretion may promote hyponatremia, as seen in many burn patients. Although we did not test this hypothesis in our patients, the mean 20% decrement in total blood volume would suggest that the elevated levels of plasma ADH are an appropriate response in an attempt to restore blood volume.

Although hypotension and increased serum osmolality, by stimulation of stretch and osmo receptors, respectively, are the most potent stimulators of ADH release, modest decrements in blood volume also may cause appreciable pituitary release of this hormone. A 10% decrease in blood volume has been previously shown to result in a two- to threefold increase in plasma ADH levels.¹⁷ In addition blood volume deficits of 10% to 15% are known to decrease the osmotic threshold for the release of ADH, although the linear relationship between plasma osmolality and plasma ADH levels is maintained. In our patients a 19% blood volume deficit resulted in a 4.5-fold increase in plasma ADH levels. The significantly decreased free water clearance and increased urine osmolality seen in our patients, as compared to the control population, document the expected influence of elevated ADH levels on the kidney.

Elevated plasma renin activity and aldosterone levels have been noted in burn patients during the postresuscitative phase.¹ As in the previously referenced ADH studies, blood volumes were not measured and the findings of elevated creatinine clearance and normal plasma tonicity were used as evidence for at least normal blood volume at the time of study. These findings, in concert with a normal plasma aldosterone decrease after a mild

volume stimulus, were interpreted to mean that the renin-angiotensin-aldosterone system remained volume responsive in burn patients but that the elevated level of function occurred because of resetting of control mechanisms. The excess renin release was attributed, at least in part, to excess sympathetic activity, which occurs following burn injury and is also known to increase renin release.¹⁸ In our patients plasma renin activity was significantly elevated compared to the control population. Plasma aldosterone levels, although elevated, were not statistically different from normal. The elevation in PRA in our patients is consistent with the anticipated increase in sympathetic activity in burn patients. It is possible that the one time measurement of fluctuating plasma aldosterone may not have been sufficient to reveal an elevated integral aldosterone level that may have been present in light of the elevated urinary K⁺/Na⁺ ratio. Nevertheless the relatively small aldosterone response to plasma renin activity has been described commonly in critically ill patients.¹⁹ Our concurrent finding of increased atrial natriuretic factor, which is known to decrease aldosterone synthesis, may explain partially this finding.^{6,20-22} Elevated urinary potassium concentrations and K⁺/Na⁺ ratios, despite slightly lower serum potassium and nondepressed urinary sodium in the patients, suggest an elevated aldosterone effect due, more likely, to a volume deficit than to sodium unavailability.

The finding of elevated atrial natriuretic factor levels does not fit entirely with our understanding of the normal stimuli for this cardiac hormone's release. Typically elevations in blood pressure and atrial distension secondary to blood volume excess are the stimuli that result in an increase in ANF release.⁵ Neither of these mechanisms were operative in our patients. Recently it has been reported that, *in vitro*, elevated levels of ADH and angiotensin added to the media with freshly excised rat atria resulted in a significant increase in ANF release.²³ Thus the elevated ADH levels documented in our patients may result in an increased release of ANF. Elevated levels of ANF have been reported following thermal injury and resuscitation.²⁴ Other investigators²⁵ have reported a correlation between heart rate and ANF release that is independent of volume. The tachycardia documented in our patients thus may be partially responsible for the el-

TABLE 6. Comparison of ADH Levels for Patients with Low and Normal Blood Volumes

	Low	Normal
% Predicted TBV	75.8 ± 2.8	91.8 ± 2.7†
ADH level (pg/mL)	7.72 ± 2.5	1.97 ± 0.26*
n	6	3

TBV, total blood volume.

* p = 0.05; † p < 0.01.

evated levels of ANF, although this mechanism has recently been disputed.²⁶ This, in turn, may have a negative effect on aldosterone secretion. Atrial natriuretic factor appears to decrease aldosterone levels by inhibiting synthesis of this hormone in the adrenal glomerulosa cells.²⁰

Except for the absence of hyponatremia, our patients are remarkably similar to those previously reported. Shirani et al.¹ studied nine burn patients in whom elevated ADH levels were documented. Those patients had hypertonic urine with a urine output of 2.7 L/day, a mean urine osmolality of 500 mosm/kg, and a mean urine sodium of 80 mmol/L (millimolar). Those values are quite comparable to those of the present study patients, who had a mean urine flow of 2.3 L/day, a urine osmolality of 656 mosm/kg, and a mean urine sodium of 70 mmol/L. The mean plasma ADH level of 6.8 pg/mL reported previously was very close to the levels documented in our patients (5.6 pg/mL). The only differences between the two patient populations were the serum sodium and osmolality: the former was 138 mmol/L in our patients compared to 130 mmol/L in the earlier study. The mean plasma osmolality of the patients in the earlier study was lower than in the patients in the present study (276 versus 286 mosm/kg). The serum sodium of 130 mmol/L was interpreted as being consistent with a free water excess indicative of increased blood volume. However those laboratory findings are also consistent with an intravascular volume deficit in association with a large intravascular sodium deficit, which may occur with excessive third space fluid losses and an osmotic diuresis prompted by urea; both circumstances occur following thermal injury.

It appears that the central problem in our cohort of patients involves mobilization of the edema fluid to the intravascular space. Five of the seven patients' weights were markedly more than their preburn weights on the day of study. In addition, because the total 24-hour intake surrounding the study period exceeded the estimated wound evaporative loss by at least maintenance fluid requirements in each patient, they were all considered to have received adequate replacement of ongoing fluid losses. Fluid administration rates were dictated by the patients' urinary output and serum sodium. In their management, decreasing urine outputs and increasing serum sodium levels were interpreted to be consistent with a contracting blood volume and resulted in an increase in the rate of relatively hypotonic intravenous fluid administration. Failure to adjust the rate was normally followed by an increase in serum BUN and creatinine levels and other signs of prerenal azotemia. After resuscitation shifts of water from the interstitial to the intravascular space normally occur secondary to differences in oncotic pressure, which normally favors water movement from the interstitial to intravascular space. Following burn injury and resuscitation, the intravascular colloid osmotic pres-

sure is low, thus decreasing the net force that determines water movement. Whether artificially increasing plasma colloid osmotic pressure during this time period would improve edema mobilization cannot be answered from these data.

Findings of increased blood flow associated with a hyperdynamic circulation (elevated cardiac output) and increased organ flow (increased effective renal plasma flow, increased wound blood flow) have previously been interpreted to indicate a normal or supranormal blood volume. Our findings of increased flow in conjunction with modest decrements in total blood volume appear to be paradoxical. The reasons for the dissociation of flow and volume may lie in the neural peripheral vascular response to injury. The effects of the markedly elevated beta adrenergic activity,¹⁸ which occurs following injury in association with what amounts to an effective arterial-venous shunt in the wound, may be enough to counterbalance the measured decrements in blood volume. Thus the decrease in peripheral vascular resistance typical of the flow phase of injury may serve to decrease afterload and raise the effective arterial capacity, which is underfilled at sites of hormone control.

The interpretation of blood volume measurements is complicated by various factors. First there is a difficulty in obtaining simultaneous measurements of RBC volume and plasma volume. The use of ⁵¹chromium-labeled RBCs represents a well-standardized and accepted method for the measurement of RBC volume.^{27,28} To obtain plasma volume estimates, one may either measure the space directly by the use of radiolabeled albumin or estimate it by the use of RBC volume and hematocrit levels. Use of labeled albumin in critically ill patients significantly overestimates plasma volumes due to the expanded volume of distribution for this molecule. Because of this plasma and total blood volumes in burned patients are usually estimated from the RBC volume and hematocrit measurements. Normal total blood volume has been reported to range from 60 to 80 mL/kg for men and 55 to 75 mL/kg for women. However, for comparison, we first expressed our measured patient values each as a percentage of the expected normal volume for that patient estimated from BSA according to previously reported regressions. As a group our patients had a total blood volume that was 81% of the predicted value. We then compared each individual patient to the reference range. Three patients had blood volumes within the normal reference range, while the remaining four (two measured twice) had blood volumes that were less than the expected range. The three patients with normal blood volumes had ADH levels that were not different from the normal controls. The patients with low blood volumes had elevated levels of ADH, the expected response based on blood volume.

It appears from our data that cardiac output and renal

perfusion in burn patients may not reflect effective blood volume status as registered at hormonal control sites. The dissociation of organ flow and hormonal response necessitates simultaneous direct measurements of blood volume to elucidate factors other than resetting of central neural control mechanisms to explain hormonal changes in the flow phase of injury. Furthermore these data indicate that in burn patients increased blood flow does not depend on increased blood volume.

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DISCUSSION

DR. D. WILMORE (Easton, Massachusetts): The group at the US Army Institute of Surgical Research have had a long-term interest in fluid regulation and water and sodium balance in burn patients. This is another interesting and provocative paper that is a continuation of work in this area that has originated from this Institute.

There are a number of things that could be added to the paper that would help us with understanding, accounts of both studies performed in the normals and those investigations done in patients, and I would just like to mention a few of these points.

First normal individuals are usually standardized in terms of diet, fluid and salt intake, and in terms of exercise and environmental conditioning when renal function tests are done. Would the authors outline their standardization that was provided for their normal controls?

Patients also should be standardized in terms of fluid intake, salt intake, whether they were ventilated, if were they receiving enteral or parenteral feedings, and the type of medication they received. This information also would be quite helpful if it could be included in the manuscript.

The US Army Institute of Surgical Research reported in an earlier paper that patients do not have full colonization of burn wounds, and that overtime colonization occurs. Could it be that the bacteria on the wound's surface elicits factors that are vasoactive and over time could change blood volume regulation? We need to know more about the microbiology of these particular patients.

Of course the crux of the contention is that we can measure blood volume using this chromium label technique, and it is a very well-established technique, but it would be good to know what the variation in the measurement was if the technique were used in normal individuals and what the reproducibility of the measurement was with successive determinations from week after week measurements. Such data would give us a good deal of confidence concerning these measurement.

Moreover it may well be that in expressing blood volume, we should express it in terms other than kilogram body weight or body surface area. As you recall these patients were edematous, and we really do not know their "true" or actual body weight. Would it be better to measure total body water and express blood volume as a unit of lean body mass or to

use bioelectrical impedance to express blood volume as a unit of lean body mass, correcting or adjusting for edema?

But if these patients were experiencing a functional volume deficit, would they respond normally to volume loading? Have the authors given blood to these patients and seen alterations in their vasoactive or salt-retaining hormones as blood is infused? It seems to me that that would be a much more dynamic type of functional measurement if it could be performed.

Finally in this modern age of biotechnology, could this whole presumed deficit be resolved by giving recombinant erythropoietin to stimulate blood volume mass, which is low in these patients?

This is an interesting and indeed a provocative paper, and as we learn more about the regulation of blood and fluid volume, I am sure that this new information will help us take better care of our critically ill patients.

DR. DONALD GANN (Baltimore, Maryland): I think this is a very important study that was very carefully executed. Part of what I have to say will echo some of Dr. Wilmore's comments, but I have a somewhat different perspective.

I also am grateful to the authors for sending me the manuscript, because it demands very careful examination. It is very meaty indeed.

I also am particularly grateful for this study, because when Dr. Shirani first suggested that inappropriate antidiuretic hormone (ADH) secretion was a feature of the burn patient, I discussed the paper and suggested that in fact it may be attributable to blood volume. Thus this is one of those rare occasions when one can actually suggest that somebody else do a study and see it carried out with the proper results. I probably should stop there.

I would note, however, that we have known since the landmark publication of Leaf and Mamby in 1950 that a small volume deficit can lead to sufficient persistent hypovolemia; so that normal subjects—in that case, Harvard medical students who were presumed normal—could drink themselves into water intoxication, implying persistent elevation of vasopressin.

In the early 1960s, Hastings, Wright, and I showed that in postoperative patients, the administration of saline could suppress vasopressin sufficiently to produce free water. That, in a less severely injured population, is the answer to Dr. Wilmore's question: namely, you can indeed turn off those hormones. Cross and others from my own laboratory, in a paper published about a year ago in the *Annals*, showed that in a group of postoperative cardiac surgical patients the counter-regulatory hormones can be suppressed by volume loading. Dr. Vaughan from Dr. Pruitt's group and others reported consistent elevation in cortisol in burn patients for as long as 30 days. This was a dominant feature of the severely injured patients.

Those observations that I have mentioned suggest to me several questions, perhaps the most important one of which is that mentioned by Dr. Wilmore: namely, what was the intake in the normal subjects as well as in the patients? The control subjects excreted in excess of 7 L of water a day. Assuming that they had normal bladder capacity and slept approximately 8 hours, their entire waking life was spent excreting large volumes of urine.

They also excreted in excess of 250 mEq sodium in a day, a very high sodium load, which probably explains their limited production of free water, but certainly does not suggest that they were eating a normal diet. Were they matched for the salt and water intake of the patients? I assume so, but this was not mentioned in the manuscript.

Does the decreased blood volume seen in the patients account for the prolonged elevation of cortisol? Cortisol, as we have shown, is probably the dominant hormone responsible for restitution of blood volume after production of an acute volume deficit.

And finally, and most important, if neither the hemodynamic status of the patient nor the urine output can adequately reflect the effective circulating volume, how do the authors propose to ascertain the adequacy of replacement in burn patients? This is particularly important because continued elevation in cortisol and in other substances responding to a volume deficit may be important mediators of continued immunosuppression and ultimately of sepsis in these highly susceptible patients.

DR. DAVID HERNDON (Galveston Texas): This fascinating paper demonstrates a remarkable, if not astounding, paradox. It really flies against traditional wisdom previously published by these authors. They

demonstrate in patients with large burns at 8 days postburn that they are hypovolemic rather than being, as we previously had thought, hypervolemic.

Despite this demonstrated hypovolemia, these patients are markedly hyperdynamic and had increased cardiac indices and renal blood flow: another paradox. They have, as previously shown, antidiuretic hormone (ADH), cortisol, and renin levels that are markedly elevated. This has previously been attributed to inappropriate ADH production in response to burn stress, but by measuring red blood cell volume with an extremely useful chromium labeling technique, it is believed that these hormonal changes are normal responses to hypovolemia.

A further paradox, however, is the finding of the elevated atrial natriuretic factor (ANF) levels. This substance is primarily controlled by atrial stretch, and hypervolemia is its usual stimulus.

These findings are puzzling, and I have several questions. The plasma volume was calculated, but not measured. It was thought to be 100% of normal. The whole of the blood volume decrease was accounted for by a decrease in red blood cell volume. In most anemias, plasma volume reciprocally increases as blood cell volume decreases. I am wondering why this did not occur in this setting.

In this study the plasma volume was calculated from the hematocrit. Why did the authors not directly measure plasma volume with a dye or radioactive technique, as I believe they have in the past?

How confident are they in these calculations of plasma volume, on which so much of their hypotheses rest?

I too was curious as to why the urine output of their controls was 300 mL/hour per 1.73 meter square, whereas it was only 87 mL for the same indices in the patients. That is a marked discrepancy. How do the authors account for the massive urine output of their controls, where they allowed water, beer, or coffee *ad libitum*?

Is it conceivable, given these huge urine outputs in the controls, that they were volume expanded, which would affect the significance, of course, of the comparisons of renin, ANF, ADH, cortisol, and, most markedly, the clearances between the two groups?

Serum albumin or colloid osmotic pressure could clearly affect these results. These values were not provided in the manuscript, and I would be curious as to what they were.

Why did you not measure blood volume in your control patients? Their urine output would indicate they were hypervolemic, of course.

Because you measured cardiac index—Swan-Ganz catheters were clearly in—did pulmonary artery wedge pressures correlate with this demonstrated hypovolemia?

Have you changed your clinical practice since the prior publication of Shirani on this subject, in which urine outputs were higher in patients and the serum sodiums were 130, as opposed to the serum sodium of 138 in your current group? Are you fluid restricting patients now and making them relatively hypovolemic? Perhaps in the earlier study, patients were normovolemic and the postulative inappropriate ADH secretion could stand.

Finally the demonstrated hypovolemia is potentially deleterious. Vasoconstriction to some organs, perhaps to the gut, may be required to maintain a hyperdynamic state in the face of hypovolemia. This could result in bacterial or endotoxin translocation from the gut. Should we be more liberal, then, in fluid loading burn patients with red blood cells or colloid during the second week postburn to reverse this demonstrated hypovolemia with its potential deleterious effects?

DR. FRANCIS D. MOORE (Boston, Massachusetts): The conservation of body water is one of the most basic and primitive responses of all land-dwelling vertebrates. Now I have always been interested in the primitive nature of much of the response to surgery and to injury. These responses have Darwinian survival significance. Once upon a time, I wrote a carefully documented chapter on that subject for a surgical textbook. Although it has been—wisely, I am sure—withdrawn from that textbook, there is a message there that should not be forgotten.

So when we call antidiuretic hormone (ADH) secretion "inappropriate," we'd better be careful. "Inappropriate" to whom, for what, in whose judgment?

As you know, Verney, the originator of all this work, thought ADH was secreted in response to elevated osmolality.

Leaf and Barter then, in a brilliant series of experiments in humans, showed that given a clear choice between maintaining volume and main-

taining osmolarity by ADH increases, the body would always prefer to restore volume. So Verney's idea had to be a little bit changed.

Also there are neural and other sensory pathways involved. David Hume, before he became a pioneer transplant, was working in this field. We did a lot of work together on this subject. Ether anesthesia is a strong stimulus to ADH, as is morphine analgesia. A bleed with prompt retransfusion immediately stimulates ADH. Finally we discovered that the first few milliliters that were lost (even the venipuncture itself) would stimulate ADH secretion. High altitude and low PO_2 will increase ADH secretion. In fact some of the headache that is seen in people at high altitude is due to excess loading of water and salt in the body and a disproportionate representation in the cerebrospinal fluid.

So we have to be very, very careful before we call ADH "inappropriate." We have got to be careful before we assign it to some one cause such as tonicity or volume, when so many things can stimulate this water-saving survival response.

In young men going to bed at night, there is a strong antidiuresis. Sadly this is not seen in older men. Just why old men lose this God-given ability to concentrate their urine and lower their voiding volume at night, I have never been able to figure out. But it has only bothered me for a few years, so there is still hope—or is there?

Finally I would like to congratulate Basil and Dr. Mason and the team at Brooke. For some years I was a member of the Surgeon General's committee that inspected that unit, and our inspections were really quite long, because I wanted to learn everything that I could while I was there! You have been leaders in burn therapy for all these years, and so far as I know, care for the biggest load of severely burned patients in the United States. That has never dimmed your interest in discovering new things that would be helpful to everybody.

So I would like to congratulate you. But take it easy on that "inappropriate" business.

DR. W. G. CIOFFI (Closing discussion): Dr. Wilmore, your first question was about the standardization of the normal volunteers. They were admitted 1 day before study and were allowed food until 6 hours before their study. They were started on IV fluids (D5 in $\frac{1}{4}$ NS) at rates that we hoped would match the IV intake in the patients, and this resulted in some of the discrepancies noted by Dr. Herndon in terms of urine output and sodium excretion.

The patients were all receiving maintenance fluids, as well as hypotonic solutions to replace their estimated evaporative losses. This allowed approximately a 10% weight loss per day of their initial weight gain.

The patients were not infected. All patients were receiving enteral feedings at the time of the study, and their fluid management was as outlined. I do not have data on the bacterial density on their wounds; no patient, however, had a wound infection before or during the study.

We did not do the chromium label study on the normal volunteers. We do have data on normals, however, which are from our Nuclear Medicine Department, which performed this part of the study, and they have consistently shown patients who should be expected to be in the normal range to be so.

Your recommendation for expressing blood volume as an index of

lean body mass is a good one, but we do not have the data available to do that.

The value of erythropoietin in these patients is not clear. Several papers presented last week at the American Burn Association demonstrated already high endogenous circulating levels of erythropoietin after injury. Whether or not the addition of exogenous erythropoietin will help to restore the red cell volume to normal is not clear.

Dr. Gann, I think I have answered your question as far as the intakes in the normal controls as compared with the patients. I agree that the deficit we saw in total blood volume may well be responsible for the prolonged elevation to cortisol levels.

You asked about what we could do to assess the adequacy of fluid replacement after resuscitation in patients, if indeed cardiac output or urine output are not going to be reliable indicators. I think we do have several things that we could follow in our second study, which we plan to undertake soon, in which we will attempt to volume load these patients, either with red cells or with saline to a normal blood volume, and we will look at cardiac output to see if it will decrease, as well as looking at O_2 consumption measured by indirect calorimetry.

Dr. Herndon, you noted the paradox of our increased atrial natriuretic factor levels. Typically atrial distension has always been thought to be a stimulus for this hormone's release, but there are also significant data in the literature suggesting that elevated sympathetic tone, tachycardia, elevated vasopressin, and aldosterone levels also lead to hormone secretion.

It also should be noted that atrial natriuretic factor (ANF) also serves to down-regulate plasma renin activity, angiotensin, and aldosterone, and it may be the elevated ANF levels that were responsible for a lack of a consistent finding of elevated aldosterone.

We did not measure plasma volume. It has been done before. We chose not to do that, because we believe there is no reliable marker to use in these patients at a time when albumin flux is continuing across into the wound, and thus radiolabeled albumin or similar markers would not give us an accurate assessment of plasma volume.

It is true that anemic patients with decreased red cell volumes increase their plasma volume to bring their blood volume back to normal. But that happens over a prolonged time and most notably in chronic renal failure patients. That is a chronic effect, and I wouldn't expect it to occur over postburn days 6, 7, or 8.

Our albumin levels were 2.2 or less in the patients. We did not measure COP levels.

There was not a good correlation between wedge pressure readings and blood volume. The mean pulmonary artery wedge pressure (PAWP) was 9. Our clinical practice has not changed since Dr. Shirani's study of several years ago.

As far as the liberal use of red cells for volume replacement, I would recommend that over the use of plasma volume expanders. We must take into consideration a report that we published several years ago, however, which did show a relationship between red cell transfusion and subsequent risk of infection, and thus we have to consider that before charging ahead and infusing many units of red cells into these patients.

Dr. Moore, I would like to thank you for your comments and couldn't agree more that the term "inappropriate" is probably inappropriate in this meeting.



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